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10/552,892	11/26/2007	Antti Haapalinna	06267.0132	4440

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EXAMINER	
RAO, SAVITHA M	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,892	HAAPALINNA ET AL.	
	Examiner	Art Unit	
	SAVITHA RAO	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/09/2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8* is/are pending in the application.

4a) Of the above claim(s) *3-6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-2 and 8 are pending.

Receipt and consideration of Applicants' amended claim set and remarks/arguments filed on 11/09/2010 acknowledged. Claim 1 is amended. Claims 3-6 remain withdrawn from consideration as being drawn towards nonelected specie and new claim 8 is added.

Applicants' arguments, filed 11/09/2010, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112 (1st Paragraph)

New Grounds of Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1,2 and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inhibiting the development of severe epilepsy in patients with head trauma, cerebral ischemia and neurosurgical operation with atipamezole, does not reasonably provide enablement for the method of inhibiting

the development of epilepsy in other patients with the varied and different types of infections. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

All of the *Wands* factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of invention and breadth of claims:

Claim 1 is drawn a method for inhibiting the development of epilepsy in patients at risk of developing epilepsy caused due to head trauma, brain ischemia, infection or neurosurgical operation by administration an effective amount of selective α_2-adrenoceptors antagonist. The breadth of the claim is extensive as it encompasses in that it encompasses a huge and varied subject population such as any person with an infection,

Relative skill of those in the art:

The relative skill of those in the art is high at least a MS or PhD level in the area of neurology.

State of the prior art/Predictability or unpredictability of the art:

The state of the prior art is such that it involves screening both *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. which compounds treat which specific disease). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic or preventive regimen on its face.

With regards to the condition of infection, infection encompasses several different types, of several different organs caused by several different microorganisms such as virus, bacteria, fungal and protozoal infections. The consequences of infection are varied depending on the type of the agent, site of infection and the extent of infection. While the state of the art with respect to the control of infectious diseases with antibacterial, antifungal, antiprotozoal agents and antibiotics are well known and predictable, treatment of infections with antiepileptic agents is unpredictable.

As taught by (Lancman et al. Epilepsy research, 25, 1996, pages 285-290). Although a history of CNS infection is not a rare finding in patients undergoing evaluation for epilepsy, the latency between the CNS infection and development of epilepsy is varied and longer for meningitis and the type of epilepsy developed by the patients infected with different organism is different. (page 288-289). Lancman et al. ,additionally teaches that the risk of unprovoked seizures in patients with prior CNS

infection is seven times higher than in general population, However, the latency period involved in the manifestation of the epilepsy following CNS infections and the type and extant of the seizure which may or may not be the same as the seizures resulting from Brain trauma or ischemia makes it very hard to treat the epileptic conditions. This is more complicated from the state of the prior art which teaches that α_2-adrenoceptors antagonist including selective α_2-adrenoceptors antagonist such as atipamezole have proconvulsant effect. (see instant specification, page 2, 1st paragraph).

Amount of guidance/Existence of working examples:

The only examples present in the instant specification are for specific α_2-adrenoceptor antagonist atipamezole in inhibiting the surgically induced status epilepticus in rats. There are no examples of activity of atipamezole in inhibition of epilepsy which results from infections. Lack of a working example is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2164.

Thus, factors such as "sufficient working examples", "the level of skill in the art", and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant claimed methods. In view of the breadth of the claims, the chemical nature of the invention, and the lack of working examples regarding the activity of the claimed compound, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate with the scope of the claims.

Thus, the specification fails to provide clear and convincing evidence in sufficient support for using the claimed compounds in the method claimed.

Genetech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors as discussed above, e.g., the amount of guidance provided and the lack of working examples to practice the claimed invention herein a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 103

New grounds of rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Puurunen et al (Neuropharmacology 40 (2001) 597-606) in view of Ginsberg et al (Stroke, 1989; 20, pages 1627-1642) as evidenced by Leker et al (Brain Research Reviews, 42, 2003, pages 187-203) (all the references already of record)

Puurunen et al. discloses that systemic administration of atipamezole facilitates recovery following transient focal cerebral ischemia in rats (abstract) Puurunen et al. discloses that atipamezole rapidly penetrates the brain and increases the release of central noradrenaline. Puurunen et al. Also discloses that atipamezole is a potent alpha2-adrenoceptor antagonist with a high alpha2/alpha1 selectivity ratio with negligible affinity for other receptors such as 5-HT and imidazoline receptors (page 598, left col., 2nd paragraph). Puurunen et al. discloses brain ischemic induction in rats and treatment of these rats with atipamezole hydrochloride in sterile water administered

once a day (1 mg/kg subcutaneously), beginning on day 2 of the ischemic induction and continuing for 10 days (page .598, methods, sections 2.1 and 2.2). Puurunen et al. discloses that atipamezole is well –tolerated over a wide range of doses and that atipamezole improved behavioral performance of ischemic rats and accordingly provides a promising pharmaceutical approach to facilitate the recovery process following cerebral ischemia (page 604, right col., last paragraph).

With respect to instant claim 8, Puurunen teaches the use of Atipamezole hydrochloride in his method and as such renders this claim obvious.

Puurunen does not teach the administration of the drug to human patient at risk of developing epilepsy.

However, animal testing in biomedical research is used as a reflection of the final outcome in humans. As disclosed by Ginsberg et al the use of physiologically regulated, reproducible animal models is crucial to the study of ischemic brain injury-both the mechanisms governing its occurrence and potential therapeutic strategies (abstract), Ginsberg additionally teaches that rodent species are readily available at low cost and are widely employed for this purpose (abstract). In addition Ginsberg teaches that Rodents have close resemblance of the cerebrovasuclar anatomy an physiology to that of higher species (page 1627, right col., 1st paragraph). Accordingly, it would have been obvious to an ordinarily skilled artisan to extrapolate the results obtained by Puurunen et al which clearly recites the beneficial effects of atipamezole as a promising pharmaceutical approach to facilitate the recovery process following cerebral ischemia. in rats to that of mammals and specifically humans and as such develop a method of

treating human patients with brain ischemia with atipamezole. An ordinarily skilled artisan will be imbued with at least a reasonable expectation of success that such a method would provide an alternative and potentially better therapeutic treatment procedure for brain ischemia.

Leker et al is used here as evidentiary document to demonstrate that cerebral ischemia leads to epileptic attack. Leker et al teaches that epileptic seizures may be the result of cerebral ischemia and may also cause brain damage and additionally, suggests that the pathological mechanisms leading to epileptic seizures are identical to those involved in cerebral ischemia (page 188, left column). Leker additionally teaches that experimental models using focal ischemia, usually obtained by occlusion of the middle cerebral artery are representative of stroke pathophysiology (page 190, right col. Last paragraph to page 191, left col. 1st paragraph). As such an ischemic patient would essentially be at risk of epileptic seizures. Therefore, when a patient with brain ischemia is treated with atipamezole, the compound will inherently inhibit the development of epilepsy upon administration. As such, the active step including the subject are in the method of Puurunen et al. i.e., the method of administration of atipamezole to a patient who is at risk of developing epilepsy, is the same as that which is instantly claimed and the method of inhibiting the development of epilepsy in such a subject will thereby be inherent to atipamezole used in the method of Puurunen. It is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In

such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph. It is also noted that "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). As such the instantly claimed mechanistic functions of the compounds to inhibit the development of epilepsy would be present in the identical compound being administered to human suffering from brain ischemia as taught by Puurunen et al. and Ginsberg et al. and would therefore elicit these effects whenever it is administered.

Response to applicant's arguments filed on 11/09/2010 and 03/10/2010

Applicant's arguments with respect to the previous rejection of the claims over Pitkanen et al., Puurunen et al and Ginsberg et al. filed on 11/09/2010 are moot in light of the withdrawal of that rejection in this action as noted above.

The rejection above of claims 1 ,2 and 8 is similar to the rejection set forth in the final action dated 10/20/2009. Since the arguments for the similar rejection set forth in the final action dated 10/20/2009 submitted by the applicants on 03/10/2010 were not previously addressed and as such will be addressed in this action.

Applicant's arguments with regards to the similar action over Puurunen et al, Ginsberg et al. and Lekar submitted on 03/10/2010 are considered but not found to be persuasive.

Applicants recite paragraphs from MPEP 2141.02 and 2112 and argue that the teachings of Leker et al. used as an extrinsic evidence in the above rejection does not rise to he requisite level of making clear that the missing descriptive matter is necessarily present in the reference, i.e. that cerebral ischemia is a risk factor for epilepsy. However, applicant is reminded that Puurunen et al. discloses the active step and the subject population as instantly claimed which is the administration of atipamezole to the patients at risk of developing epilepsy which are patients with ischemia. Lekar et al provides supportive evidence that cerebral ischemic patients are at risk of developing epilepsy. Applicant argues that examiners recitation that Leker's recitation of the epileptic seizures may be the result of cerebral ischemia does not rise to the requisite level of necessarily and inevitably". It is noted that Leker et al. necessarily provides which shows that patients with cerebral ischemia are at risk of developing epilepsy. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003) It is noted that once an examiner presents evidence or reasoning tending to show inherency, the burden shifts to the applicant to show an unobvious difference. In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the

prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph.

Conclusion

Claims 1, 2 and 8 are rejected. No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7 am to 4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached at 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA RAO/
Examiner, Art Unit 1614